REMARKS

Status of the Claims

Claims 1, 3-5, 11-14 and 18-26 were previously examined. Claims 1, 3-5, 11-14 and 18-26 are canceled; and claims 27-36 have been added.

Claims 1, 3-5, 11-14 and 18-26 are canceled.

New claim 27 has been added. Support for claim 27 is found in the Specification as originally filed at page 1, paragraph 1 and in the examples in the current Specification (*see, e.g.*, page 9 Examples 1, 2, showing increased white blood cell count and increased colony forming units respectively, and Example 4, showing increased circulation of long term culture initiating cells).

New claim 28 has been added. Support is found in the Specification at claim 4 as filed.

New claim 29 has been added. Support for claim 29 is found in the Specification at claim 3 as filed.

New claim 30 has been added. Support for claim 30 is found in the Specification at claims 2 and 3 as originally filed.

New claim 31 has been added. Support for claim 31 is found in the Specification at claim 3 as originally filed.

New claim 32 has been added. Support for claim 32 is found in the Specification at claims 9 and 10 as originally filed.

New claim 33 has been added. Support for claim 33 is found in the Specification at claim 5 as originally filed.

New claims 34-36 have been added. Support for claims 34-36 is found in the Specification at page 5, lines 18-21.

No new matter has been added.

1. Claim Rejections under 35 U.S.C. § 112, Written Description

The Examiner has rejected claim 26 as failing to comply with the written description requirement. Applicants submit that the current amendments render the Examiner's rejection moot.

2. Claim Rejections under 35 U.S.C. § 103

As a preliminary matter, the Examiner's obviousness rejection under 103(a), of canceled claim 26 should be withdrawn as claim 26 does not have a counterpart in the claims as amended.

Bahlmann et al. and Robinson et al.

The Examiner has rejected claims 1-3, 11, 13 and 17 as obvious over Bahlmann et al. (US 2005/0272634) in view of Robinson et al. (Office Action pages 5-8). Applicants respectfully traverse and submit that the Examiner has not made a *prima facie* case of obviousness because Bahlmann alone or in combination with Robinson does not teach every element of the claims.

Type of progenitor cells encompassed by Bahlmann

Applicants submit that Bahlman does not teach or make obvious the type of cells of the present invention. Bahlmann teaches stimulation and subsequent mobilization and/or differentiation of endothelial progenitor cells (EPC); specifically, "cells having the ability to differentiate into endothelial cells for stimulating vasculogenesis." (*see* [0001] and [0022]). In contrast, the present invention is directed to the mobilization of peripheral blood progenitor cells (PBPCs) that have the ability to differentiate into *blood* cells.

Consequently the endothelial progenitor cells encompassed by Bahlmann are **different** from the progenitor blood cells stimulated with the composition as claimed in claim 27. Publications by skilled artisans Cutler et al., Stem cells concise review 2001; 19:108-117; (in particular page 109, left column, lines 6-7) and Case et al., Exp. Hematological 2007 Jul 35(7):1109-18, (submitted herewith) confirm Applicant's analysis. Cutler et al., clearly indicates that the peripheral blood progenitor cells PBSCs encompassed in the present invention represent a

subpopulation of CD34+ cells. Case et al. states that human cells such as CD34+ are not endothelial progenitor cells, but distinct hematopoietic progenitor cells. Thus Bahlmann does not teach the type of cells in the claims in the present invention.

Target of Bahlmann

The critical difference between EPCs and PBPCs also highlights another essential difference between Balhmann and the present invention; namely, what is the target to which the composition is directed?

In particular, the Bahlmann composition is able to stimulate vasculogenesis, specifically, the formation of new blood vessels from said endothelial progenitor cells (*See* Bahlmann paragraph [0005]). Therefore Bahlmann's target is directed to a therapy of diseases associated with a dysfunction of endothelial progenitor cells. (*See* Bahlmann paragraph [0001]). According to Bahlmann, these diseases are hypercolesterolemia, diabetes mellitus, inflammation of vessels, endotheliosis, atherosclserosis, coronary heart diseases, myocardial ischemia, angina pectoris, age related cardiovascular disorders, ischemic disorders of the extremities, Raynaud's diseases, pre-eclampsia, pregnancy induced hypertension, chronic or acute renal failure, heart failure and wound healing etc. (*See* Bahlmann paragraph [0033]).

In contrast, the composition of the present invention is able to stimulate peripheral blood progenitor cells, thus leading to an increase in the number of circulating white blood cells, circulating colony forming blood cells or of circulating long term colony initiating blood cells.

Unlike Bahlmann, the composition of the present invention may be used in patients having undergone organ transplantation, cell transplantation, tumor chemotherapy or patients treated with myelosuppressive chemotherapy. This category of patients is completely different from that encompassed by Bahlmann. Because the patient population to be treated is different, one of skill in the art would not look to Bahlmann to solve the problem addressed by the current invention.

The type of active ingredient

In addition, the above therapeutic effect is imparted according to Bahlmann mainly and essentially by Erythropoietin (EPO) (*See* Bahlmann [0001], [0010], claims), said ingredient being optionally administered in association with at least one other active ingredient chosen from a list of compounds that are indicated as having a stimulating effect on endothelial progenitors cells (*see* [0017]) such as GM-CSF, VEGF, PlGF, statin.

By contrast according to the present invention the composition of the present invention does not contain EPO but an active ingredient consisting essentially of an association of G-CSF (and not GM-CSF as in Bahlmann) and PlGF.

Bahlmann and Robinson in Combination

The Examiner states that Bahlmann does not teach G-CSF. The Examiner relies on Robinson to provide G-CSF induced stem cell mobilization.

Robinson teaches that recombinant human granulocyte-colony-stimulating-factor (G-CSF) and granulocytes-macrophage-colony-stimulating-factor are now widely used to mobilize **hematopoietic stem cells** (HSC) (*see* Robinson, Abstract).

In view of the above analysis, Applicants submit that the Examiner's conclusion that the recognized problem in the art is the "mobilization of stem cells" as reported at paragraph [007], [0023] of Bahlmann and the Abstract of Robinson, is a distortion of the teachings of those two references.

In fact, the passage cited by the Examiner (Bahlmann paragraph [007]) affirms that stimulation of the mobilization and differentiation of **endothelial progenitor cells** represents an important novel therapeutic strategy for **"increasing neovascularisation, especially vasculogenenesis."** (Bahlmann paragraph [0007]). Likewise, the Examiner's reliance on paragraph [0022] is misplaced. At paragraph [0022] Balhmann recites a definition for endothelial progenitor cells (EPC), namely "cells which circulate in the blood stream and have the ability to differentiate to

endothelial cells." As pointed out above, the cells of Bahlmann, EPC, are **different** from peripheral blood cell progenitors of the present invention.

Applicants also submit that the result of the combination of the passages cited by the Examiner (Bahlmann paragraphs [0001], [0022], and [0023]) indicate that Bahlmann is not interested in the mobilization of stem cells in the blood stream in general, but only to the mobilization of EPC for increasing vasculogenesis (increasing the number of new blood vessels). Bahlmann's focus on the mobilization of EPC for **increasing vasculogenesis** directs one of skill in the art **away** from applying the teachings of Bahlmann to the present cell type for the diseases addressed in the present invention.

As outlined above, the results of mobilization EPC have no bearing at all with the mobilization of peripheral blood progenitor cells contemplated by the instant invention. The target of the mobilization of the **peripheral blood progenitor cells** of the present invention is to increase the number of circulating white blood cells, circulating colony forming blood cells or of circulating long term colony initiating blood cells. One of skill in the art would not look to Bahlmann because it is directed to the treatment of different cells for different diseases, as discussed above.

Applicants submit that Bahlmann teaches stimulation and subsequent mobilization of EPC by using the ***critical component*** **EPO** and only optionally other active ingredients able to stimulate endothelial progenitors cells such as GM-CSF, VEGF, PlGF, a statin. Furthermore, there is no suggestion in Bahlmann pointing to the particular association of GM-CSF and PlGF.

In summary, Bahlmann, teaches the mobilization of **different stem cells**, for a **different type of treatment**, addressed to **a different typology of patients** compared to those of the present invention **and which comprises the administration of EPO** and only optionally at least **one** other active ingredient stimulating endothelial progenitor cells selected from the above mentioned list. In view of the foregoing, Applicants are confused as to why the Examiner believes it was obvious to try PLGF and GMCSF to arrive at the present invention from Bahlmann alone, or why one of skill would combine Bahlmann with Robinson, or, even if the two were combined, why the combination would make the present invention obvious to one of skill in the art.

Robinson also fails to teach the cell type of the present invention. Robinson, teaches that "recombinant human granulocyte-colony-stimulating-factor (G-CSF) and granulocyte-macrophage-colony-stimulating-factor (GMCSF) are now widely used to mobilize **hematopoietic stem cells** (HSC)." (Robinson, Abstract). Robinson does not teach the stem cells of the present invention and thus does not remedy the failings of Bahlmann. Furthermore, Robinson does not teach the equivalency of G-CSF and GMCSF in the mobilization of peripheral blood progenitor cells.

Applicants are confused as to how Bahlmann, relating to the use of GMCSF in the mobilization **endothelial progenitor cells** (EPC), could be properly combined with the use of GMCSF and G-CSF in the mobilization of the **hematopoietic cells** of Robinson, a different type of cell, to arrive at the stimulus of peripheral blood cell progenitors. One of skill in the art would know that different cell types respond differently to various stimuli. Applicants submit that one of skill would not have been motivated to combine the teachings of Bahlmann and Robinson because of the varied cell types. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Bahlmann et al., Robinson et al., Carmeliet et al., Freireich et al. and Kadar et al.

The Examiner has rejected claims 1-4, 11, 13 and 15-17 as allegedly obvious over Bahlmann et al. and Robinson et al., as applied to claims 1-3, 11, 13 and 17, in further view of Carmeliet et al. and Freiereich et al. The Examiner has also rejected claims 1-5 and 11-17 as allegedly obvious over Bahlmann, Robinson, Carmeliet and Freiereich in further view of Kadar et al. The Examiner's detailed reasoning for this rejection appears on pages 8-10 of the Office Action, and is not reproduced here. Applicants respectfully traverse.

Applicants submit that, the combination of Bahlmann and Robinson clearly fails to teach or suggest the presently claimed invention. Applicants further submit that the combination of Bahlmann and Robinson with Carmeliet et al., Freireich et al., and Kadar does not repair the deficiencies of Bahlmann and Robinson for the arguments discussed in the previous amendment at page 9 lines 1-7. namely that:

- Carmeliet teaches the use of PLGF and treat ischemia namely a therapeutic method very similar to that disclosed by Bahlmann (see the previous item 1-B) and totally different from that contemplated in the present invention;

- Freireich teaches correlating the maximum tolerable dose of toxic substances in animal models to that in man and is silent with respect to both GCSF and PlGF.

- Kadar teaches the use of only GCSF for mobilizing peripheral mononuclear blood cells in allogeneic transplantation.

Accordingly, no prior art reference teaches the presently claimed compositions that consist essentially of PlGF and G-CSF. No prior art reference teaches the presently claimed method for stimulating **blood cell** mobilization by treating a patient with PlGF and G-CSF without additional active ingredients. It follows that even the combined teachings of Bahlmann, Robinson, Carmeliet, Freireich and Kadar fail to teach the presently claimed invention, and the Examiner has not established a *prima facie* case of obviousness. Applicants therefore respectfully request reconsideration and withdrawal of these obviousness rejections.

3. Conclusion

In view of the forgoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejections.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____

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